UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,572	03/31/2006	Paul Tardi	532552000800	3904

25225 7590 07/22/2008
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
07/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,572	TARDI ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response with/without traverse, received 4/30/08, to the restriction/election requirements, mailed 1408, electing irinotecan as the lactone ring compound species, copper as the transition metal ion species, and unilamellar liposome as the type of liposome species, is acknowledged.

Applicant's statement that claims 1-18 are readable on the elected species is acknowledged.

Status of the Claims

Claims 1-21 are currently pending in this application.

Claims 19-21 are withdrawn for being directed to non-elected subject matter.

Claims 1-18 are presented for examination.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1-5, and 8-18 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemically defined lactone active agents which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 1-5, and 8-18 are directed to encompass compounds having a lactone ring which only correspond in some undefined way to specifically instantly disclosed chemicals. None of the undisclosed lactone compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural

information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined lactone chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112,

first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-18 are rejected under 102(e) as being anticipated by Tardi et al. (US Patent 7,238,367).

Tardi et al. (US Patent 7,238,367) teach the identical liposomal pharmaceutical composition as claimed by applicant; the disclosure is similar, if not completely identical to the instant application (see reference figures 1A, 2, 4A, 4B, and 5; col 5, line 1 to col. 6, line 38; col. 14, line 10 to col. 11, line 76; and see also col. 25, Example 6; see also instant figures). Tardi et al. teach a liposomal composition comprising irinotecan, copper ions and a lipid vehicle, wherein the copper ions and iriotecan are present in a concentration within the claimed molar concentration as recited in instant claim 8, and wherein the pH of the composition is within the instant claimed physiologic pH range

(see reference figures 1A, 2, 4A, 4B, and 5). For the above reasons, claims 1-18 are found to be anticipated by the cited reference.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 103(a) as being unpatentable over Unger (US Patent 5,705,187) and Moynihan et al. (US Patent 6,740,335), in further view of Mayer et al. (US Patent 5,744,158).

Unger (US Patent 5,705,187) teaches that charged species are desirable for incorporation into lipid composition to enhance stability, wherein the materials are non-covalently associated with the lipid component (abstract; col. 17, lines 23-65, especially, col. 17, lines 49-57). Unger teaches vesicular compositions, including micelles and

liposomes comprising an aqueous carrier, a lipid and a material which is capable of stabilizing the composition (abstract). Unger teaches charged cations, including metal ions such as copper (col. 17, lines 52-57). Instant claimed invention is also directed a liposomal composition. Instant claim recites the term "transition metal ion;" claim 10 recites "Cu, Zn and Co;" claim 11 recites "Cu;" claim 16 recites "Cu +2;" these terms clearly overlap with the metal ions taught by Unger (col. 17, lines 52-57). Unger do not teach liposomal formulations comprising lactone drugs.

Moynihan et al. (US Patent 6,740,335) is added to show the general state of knowledge regarding compositions comprising lactone compounds. Moynihan et al. teach liposomal formulations comprising at least one phospholipid and a camptothecins or analog thereof (abstract). Moynihan et al. teach irinotecan, applicant's elected lactone compound species (see col. col. 6, line 2; and cols. 17-18, including Tables 1-5). Moynihan et al disclose formulations having pH ranging from 5.7 to 7.1, which overlaps with the pH limitations recited in claims 2-4 (see cols. 17-18, Tables 3-5). Claim 3 recites "at least 40 mole % of the active agent is present in the ring-closed, lactone form at physiologic pH" while claim 4 recites "at least 50 mole % of the active agent is present in the ring-closed, lactone form at physiologic pH," which are construed to overlap with the teaching of Moynihan et al. of drug loading ranging from 53-89 percent (see cols. 17-18, Tables 3-5) as the loaded drug is reasonably assumed to be in a closed-ring form (see cols. 17-18, Tables 3-5).

Mayer et al. (US Patent 5,744,158) is added to show the general state of the art regarding liposomal compositions comprising antineopastic drugs, methods of preparing

said formulations, and assays for measuring free drug. Mayer et al. disclose liposomes with toxic ionizable antineoplastic agents, such as doxorubicin, epirubicin, 5-FU, daunorubicin, mitoxanthrone (col. 1, lines 16-28). Mayer et al. teach that liposomes are completely closed lipid bilayer membranes containing an entrapped aqueous volume (col. 1, lines 43-55). Mayer et al. teach that liposomes may be unilamellar vesicles (possessing a single membrane bilayer) or multilamellar vesicles (onion-like structures characterized by multiple membrane layers, each separated from the next by an aqueous layer). Mayer et al. teach that large multilamellar vesicles (MLVS), large unilamellar vesicles (LUVs i.e. applicant's elected liposome species) and small unilamellar vesicles (SUVs) have been utilized with lipid compositions incorporating variable amounts of positively charged and negatively charged lipids in addition to phosphatidylcholine (PC) and cholesterol (col. 3, lines 38-46). Mayer et al. teach liposomes that can be about 30 nm to about 2 microns in size, preferably about 100 to 300 nm in diameter (col. 5, lines 64-66); the liposomes can contain about 50 to 200 mg/ml lipid (col. 5, line 66 to col. 6, line 1). The encapsulation of the antineoplastic agents in the liposome is from about 50% to about 100 % (col. 6, lines 1-5). Mayer et al. also teach an assay method to determine free antineoplastic agents in a liposome preparation (abstract). Also, Mayer et al. disclose that it has been established that cancer therapy employing antineoplastic agents can in many cases be significantly improved by encapsulating the antineoplastic agent in liposomes using traditional methods, rather than administering the free agent directly into the body (col. 2, lines 59-65).

Based on the teaching of Unger that it is desirable to incorporate copper ions into lipid formulations to enhance the stability of the formulation, someone of skill in the art would have been motivated to combine the teachings of the above cited references to create the instant claimed inventive concept.

Thus, a person of ordinary skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Nonstatutory Double-Patenting , or Obviousness-Type, Double-Patenting, Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending U.S. Patent Application No. 11/842, 130 in view of Moynihan et al. (US Patent 6,740,335). The above discussion of Moynihan et al. in connection with the rejection under 103 is incorporated by reference. In particular, reference claim 1 is directed to "[a] method of loading at least one therapeutic agent into a liposome in a liposome composition, the method comprising:

i) providing a composition comprising liposomes, said liposomes lacking an ionophore, in an external solution, the liposomes containing an internal solution comprising encapsulated copper or cobalt ions;

ii) adding at least one therapeutic agent to the external solution; and

iii) maintaining the agent in the external solution for sufficient time to load the agent into the liposomes, whereby said copper or cobalt ions effect said loading."

Applicant's elected liposomal formation comprises copper ions. Unlike applicant's elected liposomal formulation, the reference claims do not expressly recite irinotecan. In spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary skill in the art would deem it obvious to load any therapeutic agent onto the lipsome, including applicant's elected drug species, with reasonable predictability. Thus, the instant claimed subject matter constitute nonstatutory obviousness-type double patenting in view of Moynihan et al. (US Patent 6,740,335).

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8, 16, 17, 18, 44, and 46 copending U.S. Patent application No. 11/256,445 in view of Moynihan et al. (US Patent 6,740,335). The above discussion of Moynihan et al. in connection with the rejection under 103 is incorporated by reference. Reference claim 1 recites "[a] composition comprising liposomes containing an internal solution, the internal solution comprising encapsulated copper ions and one or more encapsulated therapeutic agents, provided that the one or more therapeutic agents do not include nucleic acids and wherein the liposomes do not comprise an ionophore, wherein the external solution and external surfaces of the liposomes contain substantially no uncomplexed copper ions, and wherein the external solution and the internal solution have substantially the same pH in the range of about 6.0 to 8.5;" reference claim 44 recites "camptothecin." Unlike applicant's elected liposomal formulation, the reference claims do not expressly recite irinotecan, and is directed to encompass a broader genus of therapeutic agents (i.e. not

limited to lactone agents). . In spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary skill in the art would deem it obvious to load any therapeutic agent onto the lipsome, including applicant's elected drug species, with reasonable predictability. Thus, the instant claimed subject matter constitute nonstatutory obviousness-type double patenting in view of f Moynihan et al.

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-42 of copending application 10/551,579 in view of Moynihan et al. (US Patent 6,740,335).

The above discussion of Moynihan et al. in connection with the rejection under 103 is incorporated by reference. Reference claim 33 recites "[a] method to deliver a synergistic therapeutically effective amount of a fluoropyrimidine/water-soluble camptothecin drug combination to a subject which method comprises administering to said subject a first composition containing a fluoropyrimidine stably associated with liposomes together with a second composition containing a water-soluble camptothecin stably associated with-iposomes wherein the ratio of the fluoropyrimidine and the water soluble camptothecin administered is synergistic, wherein said stable association maintains, for at least one hour, a synergistic ratio of said fluoropyrimidine and camptothecin in the blood when administered *in vivo,* and wherein said synergistic ratio is such that when said ratio is provided to cancer cells in an *in vitro* assay over the concentration range at which the fraction of affected cells is 0.20 to 1.00, synergy is exhibited over at least 20% of said range." Like applicant's elected liposomal

formulation, reference claim 36 recites “irinotecan (CPT-11).” Unlike applicant's elected liposomal formulation, the reference claims are directed to a synergistic formulation. To the extent that the instant claims recite the term “comprising” it is reasonably contemplated that additional active agents may be added to the composition. Thus, in spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary skill in the art would deem it obvious to load a single camptothecin drug, including applicant's elected lactone species, instead of two synergistic drugs (e.g. in cases where a patient may be allergic to the non-campthothecin) by modifying the reference method steps to arrive at applicant’s elected liposomal formulation in view of Moynihan et al. (US Patent 6,740,335).

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,10, 11, 13, 18, and 19, 20 of copending U.S. Patent application No. 10/264,538 and claims 1, 2, 10-13, and 18-20 of copending application 10/417,631, both in view of Moynihan et al. (US Patent 6,740,335).

The above discussion of Moynihan et al. in connection with the rejection under 103 is incorporated by reference. In particular, reference claim 1 of (‘538) recites “[a]composition for treating cancer in a subject which composition comprises liposomes, said liposomes having associated therewith at least a first antineoplastic agent and a second antineoplastic agent in a mole ratio of the first agent to the second agent which exhibits synergistic cytotoxic or cytostatic effect with respect to cancer cells and wherein said first and second agents are associated with said liposomes so as to maintain the administered ratio in the blood for at least one hour after administration to said subject,

and wherein said composition when administered to a subject, provides therapeutic activity greater than that which is obtained when said agents are administered in the same ratio, but are not associated with said liposomes so as to maintain ~~a non antagonistic~~ the administered ratio in the blood for at least one hour; and wherein said administered synergistic ratio is such that when said ratio is provided to cancer cells in an *in vitro* assay over the concentration range at which the fraction of affected cells is 0.20 to 0.80, synergy is exhibited over at least 20% of said range. Claim 20 recites "wherein the first agent is irinotecan (i.e. applicant's elected lactone species) and the second agent is cisplatin or carboplatin." , In spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary skill in the art would deem it obvious to load a single camptothecin drug, including applicant's elected lactone species, instead of two synergistic drugs (e.g. in cases where a patient may be allergic to the non-campthothecin) to arrive at applicant's elected liposomal formulation in view of Moynihan et al. (US Patent 6,740,335).

Similarly, reference claim 1 (of '631) recites "[a] composition for treating a condition which is cancer, an inflammatory disorder or cardiovascular disease with vasculoproliferative attributes which composition comprises particulate delivery vehicles, said delivery vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent for treating said condition in a mole ratio of the first agent to the second agent which exhibits a synergistic desired biologic effect to cells relevant to said condition, wherein said stable association maintains, for at least one hour, a synergistic ratio of said agents in the blood when administered in vivo, and which composition, when administered to a subject, provides a

therapeutic activity greater than that which is obtained when said agents are administered in the same ratio …" Unlike applicant's elected liposomal formulation, the reference claims are directed to combination formulation. In spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary skill in the art would deem it obvious to load a single therapeutic agent, including applicant's elected lactone species, instead of two drugs (e.g. in cases where a patient may be allergic to the non-campthothecin) to arrive at applicant's elected liposomal formulation in view of Moynihan et al. (US Patent 6,740,335).

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending U.S. Patent application No. 10/294,474 in view of Moynihan et al. (US Patent 6,740,335).

The above discussion of Moynihan et al. (US Patent 6,740,335) in connection with the rejection under 103 is incorporated by reference.Reference claim 1 recites [a] composition comprising liposomes that contain at least one biologically active agent wherein the ordered bilayer(s) of said liposomes consist(s) essentially of: (a) one or more vesicle forming lipids, which are phospholipids or sphingolipids such that; (b) at least 1 mol % of said bilayer(s) is phosphatidylglycerol (PG) and/or phosphatidylinositol (PI); (c) 5-20 mol % cholesterol; and (d) optionally said biologically active agent; wherein said liposomes have a mean diameter between 80-200 nm +/- 25 nm; and have a transition temperature (Tc) of at least 38°C. Unlike applicant's elected liposomal formulation, the reference claims do not recite irinotecan. In spite of the difference between the reference claims and applicant's elected formulation, a person of ordinary

skill in the art would deem it obvious to load any biologically active agent, including applicant's elected lactone species, to arrive at applicant's elected liposomal formulation in view of Moynihan et al. (US Patent 6,740,335).

The above rejections are provisional nonstatutory double patenting, or obviousness-type double patenting, rejections because the conflicting claims of the copending applications have not in fact been patented.

Claims 1-18 are also rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of US Patent 7,238,367) in view of Moynihan et al. (US Patent 6,740,335).

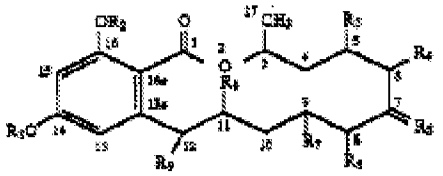
The above discussion of Moynihan et al. in connection with the rejection under 103, is incorporated by reference. In particular, reference claim 1 recites "[a] method of loading at least one therapeutic agent into a liposome in a liposome composition, the method comprising: i) providing a composition comprising liposomes, said liposomes lacking an ionophore, in an external solution, the liposomes containing an internal solution comprising encapsulated copper ions; ii) adding at least one therapeutic agent to the external solution; and iii) maintaining the agent in the external solution for sufficient time to load the agent into the liposomes." Unlike the instant claims, the reference claims are directed to a method of loading at least one therapeutic agent into a liposome and are silent regarding applicant's elected lactone compound species. In spite of this difference, a person of ordinary skill in the art would deem it obvious to select any therapeutic agent, including applicant's elected lactone species, to arrive at

applicant's elected liposomal formulation as the end product of the referenced method in view of Moynihan et al. (US Patent 6,740,335).

Relevant Art of Record

The below cited art made of record and relied upon is considered pertinent to applicant's invention.

Giese et al. (US Patent 5,728,726) is added to show the state of the art regarding formulations comprising lactone compounds. Giese et al. teach a method of selectively inhibiting a kinase comprising contacting a composition containing a kinase with a molecule of the below structure (col. 3, lines 21 to col. 5, line 9; especially col. 3, lines 30-52):



wherein:

R_1 is H, lower alkyl, or lower alkanoyl;

R_2 is H, lower alkyl, or lower alkanoyl;

R_3 and R_4 together represent a cis double bond or —O— or each of R_3 and R_4 independently represents H or OR;

R_5 is =O, =S, or —H, —OR;

R_6 and R_7 together represent a double bond or —O— or each of R_6 and R_7 independently represents H or OR;

R_8 and R_9 together represent a double bond or —O— or each of R_8 and R_9 independently represents H or OR; and

each R independently represents H, lower alkyl, or lower alkanoyl.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-

6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

16 July 2008
Examiner /C.R./

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615